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(54) Title: IMPROVED TOPICAL APPLICATION EMULSIONS

(57) Abstract

The present invention relates in general to products for topical application to the skin, and more particularly to improved stable emulsions for containing water-soluble active ingredients, such as Vitamin C, glycolic acid, etc., which may nonetheless be packaged with gelatin capsules, and which have demonstrated improved stability. In particular, the invention relates to a novel polyethylene glycol-in-oil emulsion that is compatible with gelatin capsules.

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IMPROVED TOPICAL APPLICATION EMULSIONS

BACKGROUND OF THE INVENTION

The present invention relates in general to products for topical application to the skin, and more particularly to improved, stable emulsions for carrying active ingredients, such as for example, Vitamin C, glycolic acid, etc., the combination of which may be packaged in gelatin capsules, preferably soft gelatin capsules, as well as other packaging structures. In particular, the invention in its broad embodiments relates to a novel polyethylene glycol (PEG) in oil emulsion. These emulsions are in the preferred mode of packaging compatible with gelatin capsules.

Vitamin C, i.e., ascorbic acid, is known as being suitable for preventing or treating a variety of skin pathologies or diseases. Vitamin C is described as being protective of damage caused by UV-A and UV-B radiation. Among the diseases that can be treated or prevented with Vitamin C therapy, i.e., antioxidant therapy, are UV-B radiation-induced erythema, photoaging of the skin, skin cancer, etc.

It is known in the art that unmodified gelatin capsules are incompatible with water. Accordingly, typical emulsions (Oil-in-Water or Water-In-Oil) will degrade a capsule shell made of gelatin. The present novel methods and combination of ingredients permit the formation of cosmetically acceptable emulsions that will be tolerated by gelatin capsules. One additional advantage of these PEG-in-oil emulsions, in combination with gelatin capsules, is the capacity for use of an increased percentage of water soluble actives that can be encapsulated versus typical anhydrous bases which cannot tolerate water soluble actives. For example, ingredients such as vitamin C, which would have a low

solubility in an anhydrous base, can be incorporated at higher levels using the emulsion systems of the present invention.

However, the use of PEG as the primary solubilizer for water soluble actives in gelatin capsules is not without additional problems in need of solving. In fact, from a cosmetic aesthetic perspective, the resultant emulsion carrier would in many applications be unacceptable, as PEG has a poor feel on the skin.

Thus, one difficulty overcome in developing such an emulsion system has been the modification of a predominately PEG-based product to create a better skin feel, so that it would (a) be aesthetically acceptable to the consumer, and (b) be encapsulatable in commonly used gelatin capsules.

Accordingly, one substantial advantage of the present invention is that water soluble actives can be dissolved into PEG, emulsified into an oil base with the resultant end product having a cosmetically acceptable feel, and still be compatible in ordinary gelatin capsules.

Some of the contemplated commercial uses for the present invention would be in the area of skin treatment cosmetics. Such inventive emulsions could, for example, be used for face or body products requiring certain designated water soluble actives which would be incompatible in an anhydrous base.

Other uses, advantages and objects of the improved emulsion systems of the present invention will become known to those skilled in the art upon review of the more detailed description of the present invention set forth hereinbelow.

SUMMARY OF THE INVENTION

The improved emulsions for topical application of the present invention are especially adapted for carrying a desired water soluble active ingredient which is insoluble or substantially insoluble in an anhydrous base.

In its broad parameters, the emulsions of the present invention for topical application include first and second emulsion phases, along with a dispersing agent(s) to create an emulsion therebetween.

The first emulsion phase includes polyethylene glycol (PEG) as a solvent, into which is dissolved a water soluble or substantially water soluble active ingredient, i.e., vitamin C or ascorbic acid, which is insoluble or substantially insoluble in an anhydrous base.

The second emulsion phase includes an oil, preferably selected from at least one silicone oil fluid, paraffin oils, vegetable oils, and mixtures thereof.

The invention also provides emulsions for topical administration comprising first and second emulsion phases and a dispersing agent(s). In this aspect, the first emulsion comprises PEG and a water soluble active ingredient which is insoluble or substantially insoluble in an anhydrous base. The second emulsion in this aspect comprises at least one silicone oil fluid.

Testing has shown that the improved topical application emulsions of the invention are suitable for forming stable vitamin C and other topical application products, which may be formulated with or without up to approximately 10% water, and which prove to have an acceptable stability.

The improved topical application emulsions of the present invention may be preferably applied to the skin of an individual in a gelatin capsule, which surrounds and encloses the emulsion, and which may be packaged therein according to known encapsulation methods. Particularly preferred gelatin capsules for use in the invention are "twist-off" gelatin capsules.

The invention further encompasses compositions and methods for treating and/or preventing skin damage caused by exposure to ultraviolet-A (UV-A) and ultraviolet-B (UV-B) radiation, including solar radiation. The inventive compositions include vitamin C dissolved or suspended in the topical emulsions of the invention. Further, such compositions are preferably administered to an individual or patient by way of a soft gelatin "twist-off" capsule. A gelatin capsule is a particularly preferred means for administering the vitamin C topical emulsion since the gelatin capsule prevents or decreases the oxidation of vitamin C by oxygen in the environment. Thus, the invention provides methods for antioxidant skin therapy, and specifically methods for treating or preventing UV-B radiation-induced erythema, photoaging of the skin, skin cancer, etc.

Further details and the substantial advantages of the improved topical application emulsions of the present invention will become more readily apparent to those skilled in the art upon review of the following detailed description of preferred embodiment, brief description of the drawing, the examples thereof and the appended claims.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graph showing stability of vitamin C in vitamin C containing emulsions after 3 months at various temperatures, and comparing formulations made with no water versus 5% water.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The improved emulsions for topical application of the present invention are especially adapted for carrying at least one desired water soluble active ingredient that is insoluble or substantially insoluble in an anhydrous base.

Preferred embodiments of the emulsions of the present invention for topical application include first and second emulsion phases, along with a dispersing agent(s) to create an emulsion therebetween, utilizing procedures which are described in greater detail in the Examples set forth below.

In a particularly preferred embodiment, the first emulsion phase hereof includes polyethylene glycol as a solvent, and ascorbic acid (vitamin C) which is insoluble or substantially insoluble in an anhydrous base, and which may be preferably dissolved into the polyethylene glycol solvent.

The second emulsion phase comprises an oil or mixtures of oils. Suitable oils include silicone-derivative silicone oil fluids, paraffin oils, vegetable oils and mixtures thereof. A preferred second emulsion phase comprises at least one silicone-derivative silicone oil fluid, and an oil selected from the group consisting of paraffin oils, vegetable oils and mixtures thereof, some selected examples of which are set forth hereinafter.

In another preferred embodiment, the first emulsion phase includes polyethylene glycol, a water soluble active ingredient

which is insoluble or substantially insoluble in an anhydrous base, and which may be preferably dissolved into the polyethylene glycol. In this embodiment, the second emulsion phase comprises a silicone-derivative silicone oil fluid.

The first emulsion phases of the invention may be solutions, suspensions, or dispersions of the active ingredient in the polyethylene glycol. Thus, the active ingredient may be substantially insoluble in the polyethylene glycol phase, i.e., the first emulsion phase.

As used herein, the term "gelatin compatibility" means no adverse interaction of the fill material with the gelatin capsule.

Actual testing by the inventors of the present invention has shown that the applicants' improved topical application emulsions are suitable for forming stable vitamin C topical application products, which may be formulated with or without up to approximately 10% water, and which prove to have an acceptable stability. Other active ingredients have similarly been formulated into stable and useful emulsions according to the principles and teaching of the present invention.

By "stable vitamin C topical emulsion application product" and "stable topical application emulsion" are meant topical application emulsions that do not exhibit creaming, sedimentation, or phase separation.

It has been discovered that there is surprisingly little decomposition of vitamin C in the inventive topical application emulsions.

In one preferred embodiment, for example, the quantity of vitamin C which may be formulated for use in the improved emulsions of the present invention may comprise from about 0.1 to

10, more preferably from about 1.5 to 5, and most preferably about 1.5, weight percent of the total emulsion.

In some preferred embodiments, the first emulsion phase of the improved topical application emulsions invention may further include glycerin, and may also include water up to approximately 10 weight percent by total. However, water, and especially at elevated temperature levels, adversely effects the integrity of gelatin capsules since gelatin is water soluble. Accordingly, when the topical application emulsions are intended for encapsulation in gelatin capsules, the use of substantial amounts of water in the emulsions of the present invention must be closely monitored. The first emulsion phase may also include sodium chloride, and other ingredients, as described in the Examples hereof.

The second emulsion phase may, in addition to including at least one silicone-derivative silicone oil fluid, also contain a paraffin oil such as, for example, mineral oil and/or a vegetable oil.

The polyethylene glycol of the first phase of the improved topical application emulsions of the present invention may be included in amounts of approximately 20-80, and preferably 20-50, weight percent in preferred embodiments.

Suitable polyethylene glycols for use in the topical application emulsions have molecular weights of from about 200 to 6000, and preferably from 400 to 1000.

In addition to vitamin C, other representative water soluble active ingredients include, for example, glycolic acid, MFA fruit complex, other active ingredients, and mixtures thereof, in amounts of up to about 20 weight percent.

One dispersing agent suitable for use in the improved topical application emulsions of the present invention is a polysorbate. Representative polysorbates include Tween 20, a product of ICI Corporation described as a Polysorbate 20, and Tween 80, described as a Polysorbate 80.

The silicone-derivative silicone oil of the second phase of the present invention may comprise approximately 0-50, and preferably 0-40, weight percent of the final topical emulsion. As used herein the term "silicone derivative silicone oil" refers to one or more ingredients of the kind generally known to those skilled in the art as "silicon oil." Examples without limitation include:

Silicone Fluids 244, 245, 344, 345	Cyclomethicone
Silicone Fluid Q2-5200	Laurylmethicone Copolyol
Silicone Fluid 3225C	Cyclomethicone and Dimethicone Copolyol
Abil WE09	Polyglyceryl-4 Isostearate and Cetyl Dimethicone Copolyol and Hexyl Laurate
Dow Corning 200 (various viscosities)	Dimethicone
Dow Corning 1401 Fluid	Cyclomethicone and Dimethiconol
Dow Corning 1403 Fluid	Dimethicone and Dimethiconol

The improved topical application emulsions of the present invention are set forth in the following Examples.

Preparation of Emulsions

The emulsions are made according to techniques known to those skilled in the art. Preservative and fragrance may optionally be added to the resulting emulsion formulations.

Once the appropriate emulsion is formulated, it can be encapsulated into conventional soft gelatin capsules in accordance with the rotary die process. Alternatively, the emulsions can be

appropriately encapsulated in hard shell gelatin capsules as well as soft gelatin capsules.

Unless noted otherwise, the components listed for each of the formulations described in the following examples are indicated in parts by weight.

EXAMPLES 1, 2, AND 3

	Example 1 (RDO95-51-2)	Example 2 (RDO95-50-1A)	Example 3
Phase I			
PEG-400	68.25	63.24	64.75
Vitamin C-Ascorbic Acid	1.50	1.50	1.50
Glycerin-USP	5.00	5.00	5.00
Water	-	5.00	5.00
Sodium Chloride	-	0.25	0.25
Phase II			
Silicone Fluid 245	15.00	15.00	15.00
Silicone Fluid 3225C	9.00	9.00	9.00
Tween-20	1.50	1.50	1.50
5-Freeze Thaw Cycles	Acceptable	Acceptable	Acceptable
40°C Oven Stability	Acceptable	Acceptable	Acceptable
Room temperature Stability	Acceptable	Acceptable	Acceptable
Gelatin capsule compatibility	Acceptable	Acceptable	Acceptable

The emulsions of Examples 1, 2 and 3 were made according to blending methods and procedures known to those skilled in the art.

The stability of vitamin C in the Example 1 and Example 2 formulations in terms of the percent by weight of active vitamin C remaining in the formulation after exposure to various temperatures for 90 days is shown in Figure 1.

EXAMPLES 4 and 5

	Example 4	Example 5
Phase I		
PEG-400	58.75	36.00
Vitamin C-Ascorbic Acid	1.50	1.50
Glycerin-USP	-	5.00
Ethoxylated-26 Glycerin	-	13.25
Water	8.00	8.80
Sodium Chloride	0.25	0.25
Pfaffia extract	-	0.28
Pycnogenol	-	0.14
Ecchnesia Extract	-	0.28
Phase II		
Mineral oil	-	25.00
Dow Corning Fluid 244	15.00	2.00
ABIL WE 09	-	5.00
Tween-20	2.50	-
Dow Corning Fluid 3225C	9.00	-
Borage Oil	-	1.00
Vit-E Linoleate	-	0.50
Vit-A Palmitate	-	0.50
Crodoram Rhatania "O"	-	0.33
Crodoram Nut "O"	-	0.16
Caroplex	-	0.01
5-Freeze Thaw Cycles	Acceptable	Acceptable
40°C Oven Stability	Acceptable	Acceptable
Room temperature stability	Acceptable	Acceptable
Gelatin capsule compatibility	Acceptable	Acceptable

Stable PEG/Silicone Cream Formulations

Ingredient	Example 6 (RD091-118-2)
Phase 1:	
Transcutol	18.95
PEG-1000	15.10
PEG-400	15.20
Glycerin-USP	5.00
Water	2.00
Glycolic Acid	1.00
MFA Fruit Acid	3.00
Germal 115	0.30
Phase 2:	
Synchrowax HR-C	3.00
D/C Silicone 345	20.55
D/C Silicone 3225C	11.50
D/C Silicone 556	2.00
Tween-20	2.00
Liquipar Oil	0.10
Fragrance F94-238	0.30
5-Freeze Thaw Cycles	Acceptable
40°C Oven Stability	Acceptable
Room temperature stability	Acceptable
Gelatin capsule compatibility	Acceptable

Mineral Oil/PEG Emulsions

Ingredient	Example 7 (RD095-31-1)	Example 8 (RD095-40)
Phase I:		
PEG-400	53.55	36.00
Ethoxylated-7 Glycerin	-	13.25
Glycerin-USP	5.00	5.00
Water	7.70	8.00
Sodium Chloride	0.25	0.25
Vitamin-C (Ascorbic Acid)	1.50	1.50
Pfaffia/Ecchenesia/ Pycnogenol	-	1.25
Phase II:		
Mineral Oil	25.00	25.00
D/C Fluid 244	2.00	2.00
Abil WE09	5.00	5.00
Borage Oil	-	1.00
Vit-E Linoleate	-	0.50
Vit-A Palmitate	-	0.50
Rhatania extract	-	0.50
Crodoram Nut "O"	-	0.25
5-Freeze Thaw Cycles	Acceptable	Acceptable
40°C Oven Stability	Acceptable	Acceptable
Room temperature Stability	Acceptable	Acceptable
Gelatin capsule compatibility	Acceptable	Acceptable

Vegetable Oil/Silicone Emulsions

Ingredient	Example 9 (RD095-39-1)	Example 10 (RD095-39-2)
Phase I:		
PEG-400	53.55	36.00
Ethoxylated-7 Glycerin	-	13.25
Vitamin-C (Ascorbic Acid)	1.50	1.50
Glycerin	5.00	5.00
Water	7.70	8.00
Sodium Chloride	0.25	0.25
Phase II:		
Olive Oil	25.00	25.00
Silicone Fluid 244	2.00	2.00
Abil WE09	5.00	5.00
Borage Oil	-	2.00
5-Freeze Thaw Cycles	Acceptable	Acceptable
40°C Oven Stability	Acceptable	Acceptable
Room temperature Stability	Acceptable	Acceptable
Gelatin capsule compatibility	Acceptable	Acceptable

The following table lists the source and generic name of various materials employed or suitable for use in the compositions of the invention.

Ingredient	Source	Generic Name
PEG-400, PEG-600, PEG-1000	Union Carbide	Polyethylene Glycol
Silicone Fluids 244, 245, 344, 345	Dow-Corning	Cyclomethicone
Silicone Fluid 3225C	Dow-Corning	Cyclomethicone and Dimethicone Copolyol
Tween-20	ICI Americas	Polysorbate-20
Protochem GL-7, GL-26	Protameen Chemical	Ethoxylated-7 Glycerin and Ethoxylated-26 Glycerin
ABIL WE-09	Goldschemidt	Polyglyceryl-4 Isostearate and cetyl Dimethicone Copolyol and Hexyl Laurate
Down-Corning Fluid 200	Dow-Corning	Dimethicone
Dow-Corning Fluid 1401	Dow-Corning	Cyclomethicone and Dimethiconol
Dow-Corning Fluid 1403	Dow-Corning	Dimethicone and Dimethiconol
Ceraphyl 31	ISP-Vandyk	Lauryl Lactate
Scheremol DIA	Scher and Co.	Diisopropyl Adipate
MFA-Complex	Barnett and Co.	Alpha hydroxy Acid Complex
Dry-Flow PC	National Starch	Aluminum Starch Octylsuccinate
Syncrowax HR-C	Croda	Glyceryl Behenate
Crodoram Rhatania "O"	Croda	Rhatania Root Extract
Crodoram Nut "O"	"	Walnut Extract
Caroplex	Quest	Caroteen Mixture
Pfaffia	NAT-TROP	Pfaffia extract
Echenesia extract	East Earth herb	Coneflower extract
Pycnogenol	TAAG and Co.	Martime Pine extract
Borage Oil	Cannamino and Co.	Borage Oil
Vitamin E Linoleate	Hoffman-LaRoche	Tocopheryl linoleate
Vitamin E Palmitate	Hoffman-LaRoche	Retinyl palmitate

The basic and novel characteristics of the improved methods, compositions of matter, and combination of ingredients of the present invention will be readily understood from the foregoing disclosure by those skilled in the art. It will become readily apparent that various changes and modifications may be made in the form, construction and arrangement of the improved formulations of the present invention, and in the steps of the inventive methods hereof, which various respective inventions are as set forth hereinabove without departing from the spirit and scope of such inventions. Accordingly, the preferred and alternative embodiments of the present invention set forth hereinabove are not intended to limit such spirit and scope in any way.

WHAT IS CLAIMED IS:

1. In an improved topical application emulsion for carrying ascorbic acid, the improvement comprising:

an emulsion of first and second emulsion phases, and a dispersing agent;

said first emulsion phase including, as a solvent, polyethylene glycol, and ascorbic acid; and

said second emulsion phase comprising an oil.

2. The emulsion of claim 1 where the oil is selected from the group consisting of silicone-derivative silicone oil fluids, paraffin oils, vegetable oils and mixtures thereof.

3. The emulsion of claim 2 where the oil comprises at least one silicone-derivative silicone oil fluid, and an oil selected from the group consisting of paraffin oils, vegetable oils and mixtures thereof.

4. The improved emulsion of claim 1 further comprising a gelatin capsule surrounding and enclosing said emulsion.

5. The improved emulsion of claim 1 wherein said vitamin C initially comprises approximately 0.1 to 10 weight percent of the total emulsion.

6. The improved emulsion of claim 1 wherein said first emulsion phase further comprises glycerin.

7. The improved emulsion of claim 1 wherein said first emulsion phase further comprises water.

8. The improved emulsion of claim 5 wherein said water comprises less than approximately 10 weight % of the total emulsion.

9. The improved emulsion of claim 1 wherein said second emulsion phase further comprises mineral oil.

10. The improved emulsion of claim 1 wherein said polyethylene glycol comprises approximately 20-80 weight percent.

11. The improved emulsion of claim 1 wherein said dispersing agent comprises a polysorbate.

12. The improved emulsion of claim 2 wherein said silicone-derivative silicone oil comprises approximately 0-50 weight percent.

13. The improved emulsion of claim 2 wherein said silicone-derivative silicone oil is selected from the group consisting of:

Cyclomethicone
Laurylmethicone Copolyol
Cyclomethicone and Dimethicone copolyol
Polyglyceryl-4 Isostearate and Cetyl Dimethicone Copolyol and Hexyl Laurate
Dimethicone
Cyclomethicone and Dimethiconol
Dimethicone and Dimethiconol.

14. The improved emulsion of claim 1 wherein said oil has physical properties sufficient to provide a viscosity to said emulsion which is at least partially spreadable upon and into the skin when applied.

15. The emulsion of claim 14, where the oil is selected from the group consisting of silicone-derivative silicone oil fluid, paraffin oils, vegetable oils and mixtures thereof.

16. The emulsion of claim 15, where the oil comprises at least one silicone-derivative silicone oil fluid, and an oil selected from the group consisting of paraffin oils, vegetable oils and mixtures thereof.

17. An improved emulsion for carrying water soluble active ingredients which are insoluble in an anhydrous base comprising:

an emulsion of first and second emulsion phases, and a dispersing agent;

said first emulsion phase including, as a solvent, polyethylene glycol, and a water soluble active ingredient which is insoluble in an anhydrous base dissolved into said polyethylene glycol solvent; and

said second emulsion phase comprising a silicone-derivative silicone oil fluid.

18. The improved emulsion of claim 17 further comprising a gelatin capsule surrounding and enclosing said emulsion.

19. The improved emulsion of claim 17 wherein said water soluble active ingredient comprises vitamin C.

20. The improved emulsion of claim 17 wherein said vitamin C initially comprises approximately 0.1 to 10 weight percent of the total emulsion.

21. The improved emulsion of claim 17 wherein said first emulsion phase further comprises glycerin.

22. The improved emulsion of claim 17 wherein said first emulsion phase further comprises water.

23. The improved emulsion of claim 20 wherein said water comprises less than approximately 10 weight % of the total emulsion.

24. The improved emulsion of claim 17 wherein said second emulsion phase further comprises mineral oil.

25. The improved emulsion of claim 17 wherein said second emulsion phase further comprises a vegetable oil.

26. In an improved topical application emulsion for carrying ascorbic acid, the emulsion being suitable for encapsulation in gelatin capsules, the improvement comprising:

an emulsion of first and second emulsion phases, and a dispersing agent;

said first emulsion phase including, as a solvent, polyethylene glycol, and ascorbic acid; and

said second emulsion phase comprising an oil.

27. The improved emulsion of claim 26 wherein said first emulsion phase further comprises up to about 10% water based on the weight of the emulsion.

28. The improved emulsion of claim 26 wherein said second emulsion phase further comprises a second oil which is mineral oil.

29. A soft gelatin capsule comprising a shell and an emulsion for carrying water soluble active ingredients which are insoluble in an anhydrous base, the emulsion comprising:

first and second emulsion phases, and a dispersing agent;

said first emulsion phase including, as a solvent, polyethylene glycol, and a water soluble active ingredient which is insoluble in an anhydrous base dissolved into said polyethylene glycol solvent; and

said second emulsion phase comprising a silicone-derivative silicone oil fluid.

30. The gelatin capsule of claim 29 wherein said water soluble active ingredient comprises vitamin C.

31. The gelatin capsule of claim 30 wherein said vitamin C initially comprises approximately 0.1 to 10 weight percent of the total emulsion.

32. The gelatin capsule of claim 29 wherein said first emulsion phase further comprises glycerin.

33. The gelatin capsule of claim 29 wherein said first emulsion phase further comprises up to about 10% water based on the weight of the emulsion.

34. The improved emulsion of claim 31 wherein said water comprises less than approximately 10 weight % of the total emulsion.

35. The gelatin capsule of claim 29 wherein said second emulsion phase further comprises mineral oil.

36. The gelatin capsule of claim 29 wherein said second emulsion phase further comprises a vegetable oil.

37. A soft gelatin capsule comprising:

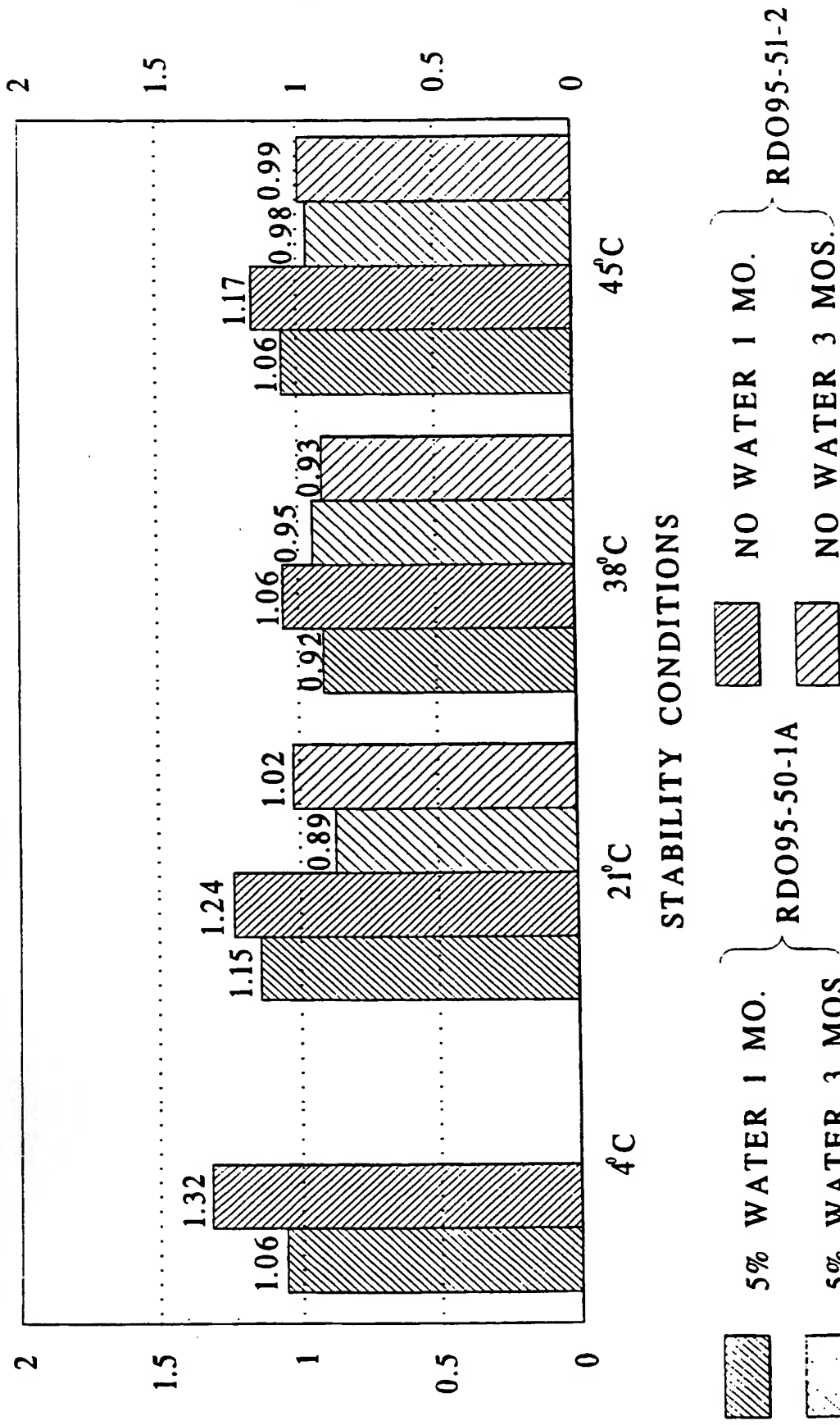
a gelatin shell; and

a fill material provided within the shell,

the fill material being an emulsion comprising from about 0.1 to 10% by weight of ascorbic acid based on the weight of the fill material, polyethylene glycol as a solvent, and an oil.

38. A gelatin capsule according to Claim 37, further comprising from about 0.5 to 10% of water in the fill material, based on the weight of the fill material.

FIG. 1



INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/US 96/01627

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 107 085 (WARNER-LAMBERT) 2 May 1984 see page 2, line 22 - page 8, line 31; claims 1-4	1-4, 26-29

Y	US,A,4 983 382 (J. M. WILMOTT ET AL) 8 January 1991 see claim 1	1-4, 26-29

A	US,A,4 767 741 (J. A. KOMOR ET AL) 30 August 1988 see claim 1	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 July 1996	16 July 1996 (16.07.96)

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Voyiazoglou, D

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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